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CASE REPORT

Successful Treatment of Ixekizumab-Induced Paradoxical Eczematous Reaction with JAK Inhibitors: A Case Report

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Abstract: With the widespread long-term use of biologics in plaque psoriasis, reports of paradoxical eczema caused by interleukin-17A (IL-17A) monoclonal antibodies are increasing. This paradoxical eczema (PE) can occasionally require termination of biologic treatment, which may result in suboptimal management of psoriasis and increased risk of disease flare-ups. In the context of PE, therapeutic strategies should prioritize agents with dual efficacy against both the primary inflammatory process and paradoxical dermatitis, such as Janus kinase (JAK) inhibitors, which modulate key cytokine pathways implicated in both conditions. This report describes a novel case of ixekizumab (IXE)-induced paradoxical eczema that was effectively managed using a sequential JAK inhibitor strategy: initial intervention with abrocitinib (100 mg daily for 2 weeks) achieved significant symptom control, followed by 90% lesion clearance after transitioning to upadacitinib (15 mg daily). Throughout the 4 weeks therapeutic course, no tuberculosis reactivation was observed.

Keywords: ixekizumab, JAK inhibitor, upadacitinib, psoriasis, paradoxical eczema

Introduction

Anti-IL-17A therapies have revolutionized the management of psoriasis by achieving unprecedented clinical responses.[1] However, emerging evidence reveals a spectrum of treatment-associated adverse events, most notably paradoxical reactions (PRs) – defined as de novo emergence or exacerbation of immune-mediated disorders following biologic initiation. Cutaneous manifestations predominate these reactions, encompassing eczematous reactions (E-PRs), lupus-like cutaneous lesions (L-PRs), sarcoidosis-like granulomatous inflammation (S-PRs), immune-mediated alopecias, neutrophilic dermatoses (pyoderma gangrenosum, Behçet-like ulcerations), interface dermatitides (lichenoid eruptions, vitiligo), granulomatous disorders (granuloma annulare, hidradenitis suppurativa), autoimmune bullous diseases (bullous pemphigoid, pemphigus) and psoriatic disease modifications (phenotypic shifts, paradoxical worsening).

E-PRs typically manifest within the first 4 months of anti-IL-17A therapy initiation. The clinical presentations demonstrate remarkable heterogeneity, ranging from classic generalized atopic dermatitis (AD)-like eruptions to distinct morphological patterns including but not limited to facial erythematous dermatitis, palmoplantar dyshidrotic eczema and nummular eczematous plaques.[2] E-PRs occurred in 2.2% of patients receiving IL-17 inhibitors.[3]

Some patients with mild to moderate paradoxical eczematous respond to discontinuation of current biologic and topical corticosteroids. Sometimes it is inadequately controlled by the application systemic immunosuppressants (eg, methotrexate, cyclosporine) or alternative pathway inhibitors.[4]

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We report the first documented case of ixekizumab-induced paradoxical eczema successfully treated with selective JAK1 inhibitors (abrocitinib and upadacitinib), achieving sustained remission without tuberculosis reactivation in a patient with prior ixekizumab-associated active tuberculosis history.

Case Presentation

A 61-year-old male with refractory psoriasis vulgaris was initiated on IXE (80 mg subcutaneously). His medical history included allergic rhinitis and type 2 diabetes mellitus. Following 10 cumulative doses, he developed secondary tuberculosis, necessitating discontinuation of IXE. After completing a 2-month course of standard anti-tuberculosis therapy (rifampicin, isoniazid, ethambutol, and pyrazinamide), IXE was re-administered on 19 January 2024. Pulmonary tuberculosis manifestations improved after six months of anti-tuberculosis treatment. However, 16 doses after IXE reinitiation, he presented with multiple erythematous papules, plaques, erosions, and exudative lesions involving the scalp, face, trunk, and extremities. IXE was discontinued, and tripterygium wilfordii glycosides (TWG) (20 mg three times daily) were trialed concurrent with topical desonide 0.05% cream twice daily to affected areas for 4 weeks without clinical improvement (Figure 1).

Subsequent treatment with abrocitinib (100 mg daily) resulted in significant resolution of truncal lesions within 2 weeks. However, psoriasis recurred 7 days after abrocitinib cessation. A single 80-mg dose of IXE was administered but triggered an aggressive paradoxical eczematous reaction (Figure 2A–C). IXE was permanently withdrawn, and upadacitinib (15 mg once daily) was initiated as replacement therapy for a 28-day course, leading to marked improvement in all lesions within 4 weeks, with no adverse events observed (Figure 2D–F). Laboratory findings showed complete blood count, C-reactive protein, erythrocyte sedimentation rate, creatine kinase, liver/renal function, IL-6, IL-4, IL-2, IL-10, IFN-γ, TNF-α, and D-dimer were normal. Hepatitis B serological panel, hepatitis C antibody, and HIV antibody were all negative. Measured serum IgE levels pre-treatment 166.4 IU/mL (reference range <100 IU/mL) and post-treatment 115.2 IU/mL. Serum IgM levels pre-treatment 0.4 g/L (reference range 0.6–2.6 g/L) and post-treatment 0.508 g/L. The Reflectance confocal microscopy (RCM) (Figure 3A and B) and dermoscopic (Figure 3C) characteristics were illustrated.

Discussion

Moderate-to-severe psoriasis, a chronic systemic immune-mediated inflammatory disorder, is associated with substantial comorbidities.[5,6] Given its lifelong disease trajectory, psoriasis management necessitates therapeutic strategies supported by longitudinal safety and tolerability data to optimize risk-benefit assessments in clinical decision-making. Ixekizumab, a humanized IgG4 monoclonal antibody with picomolar affinity for IL-17A, mechanistically inhibits this proinflammatory cytokine's interaction with its receptor. It is approved for the treatment of moderate-to-severe plaque psoriasis based

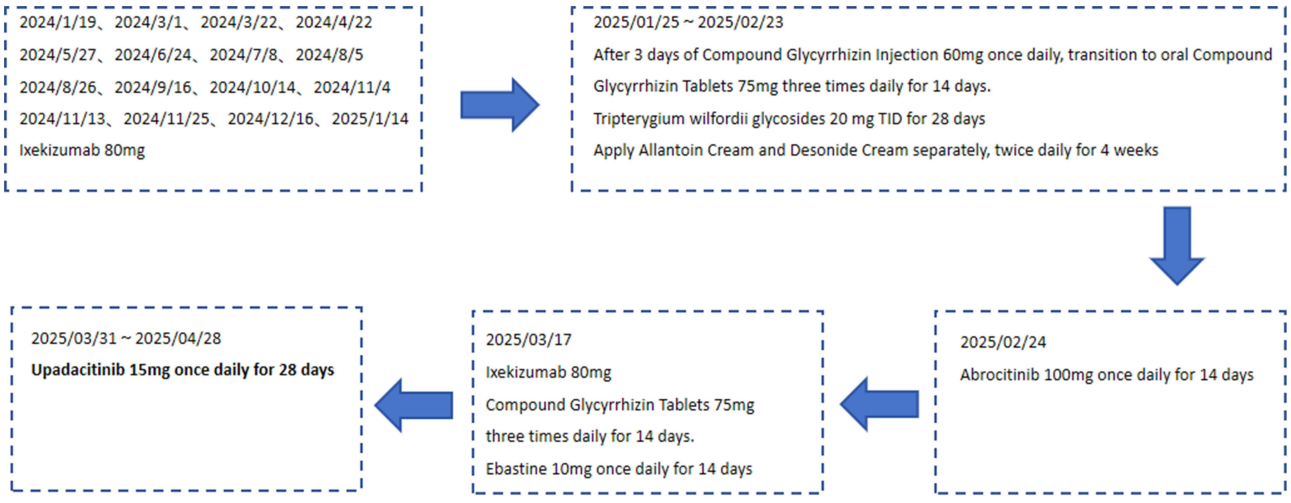

Figure 1 Treatment Timeline.

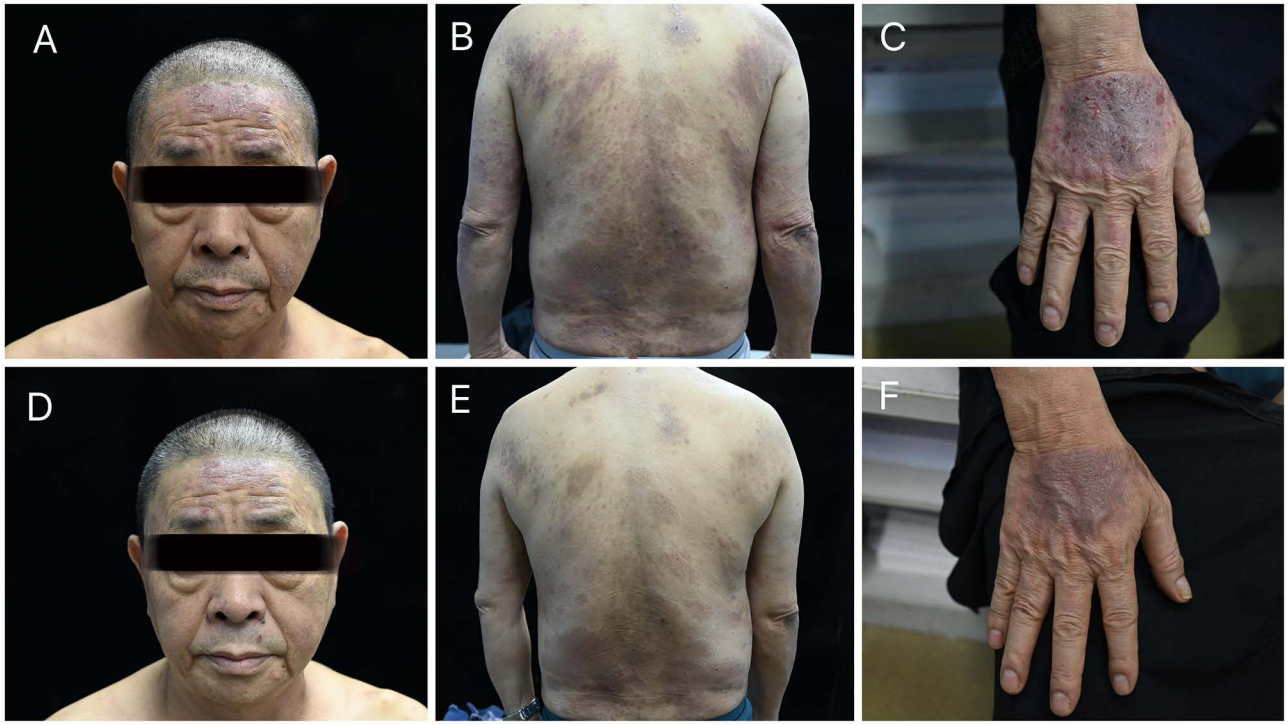

Figure 2 (**A**–**C**) Multiple erythematous papules, plaques, erosions, and exudative lesions involving the scalp, face, trunk, and extremities after IXE treatment. (**D**–**F**) Significant clinical improvement was observed in both face, truncal and extremity lesions following 4 weeks of upadacitinib therapy.

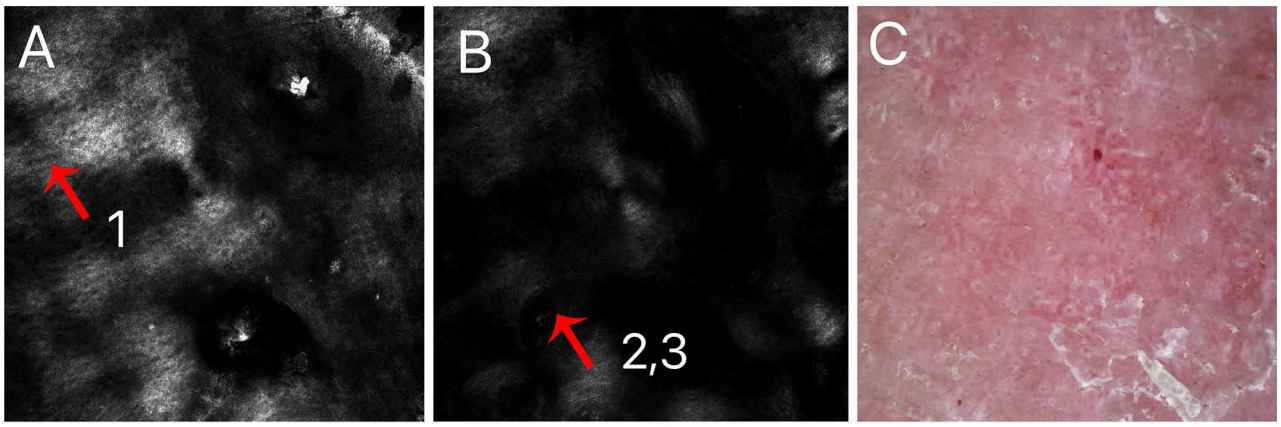

Figure 3 (**A** and **B**) RCM of the forehead skin lesion after upadacitinib therapy. (1) Acanthosis with intercellular edema in the stratum spinosum; (2) Dilatation and architectural distortion of superficial dermal vasculature accompanied by congestion; (3) Periductal lymphocytic infiltrates. (**C**) Dermoscopic of the forehead skin lesion after upadacitinib therapy. Multiple punctate and globular vessels setting against a dark red background. Focal distribution of white to yellowish-white scales, some areas exhibiting fibrous white structures. Poorly demarcated transition zone between lesion and surrounding skin.

on the sustained efficacy and favorable safety profile demonstrated across the UNCOVER program (NCT01474512, NCT01597245, NCT01646177).[7]

Infection represents the most frequently reported adverse event (AE) associated with IXE therapy in both clinical trials and post-marketing surveillance. Allergic reactions and hypersensitivity events demonstrate temporal dynamics, with higher incidence during the initial treatment year followed by stabilization or gradual decline in subsequent years.[8] The dermatological AE profile of IL-17 inhibitors warrants special consideration. Pooled data from randomized controlled trials (RCTs) and real-world evidence indicate eczematous lesions occur in 2.2–12.1% of psoriasis patients receiving IL-17 blockade.[4,9] Comparative analyses of IXE versus placebo, etanercept, and ustekinumab revealed no

statistically significant differences in incidence rates (IR per 100 patient-years) of eczematous reactions across treatment groups.[10] Systematic review data identify secukinumab (SEC) as the biologic most frequently associated with eczematous eruptions in psoriatic patients,[11] with median time-to-onset of 109 days (range: 5–1597 days) following treatment initiation.[4] Our case presentation added to this clinical spectrum, featuring a patient with pre-existing atopy (elevated serum IgE levels). This observation supported the hypothesis that IL-17 inhibition may predispose to eczema-like inflammation within psoriatic lesions, particularly in immunologically susceptible individuals. While epidemiological studies specifically investigating the atopy-PE association in psoriasis populations remain lacking, existing literature demonstrates similar associations in inflammatory bowel disease (IBD) patients receiving biologic therapies.[12] Notably, Burlando et al documented atopic-like dermatitis following SEC administration even in non-atopic individuals, with accompanying eosinophilia or IgE elevation observed in 38% (9/24) of cases.[11,13]

The precise mechanisms underlying paradoxical eczema remain incompletely understood. Current hypotheses center on the immunological interplay between Th1 and Th2 pathways. When Th1 responses are suppressed (eg, via IL-17 or TNF-α inhibition), a compensatory Th2 polarization may occur, potentially explaining the emergence of eczematous reactions.[14] Notably, Stoffel et al demonstrated that TNF-α inhibitor-induced eczematous eruptions exhibit significantly elevated IL-22 expression compared to anti-TNF-α-induced psoriasiform lesions, conventional psoriasis plaque and classic atopic eczema lesions. This is particularly relevant as IL-22 promotes epidermal hyperplasia, impaired keratinocyte differentiation and spongiosis formation.[15] However, the IL-22 hypothesis requires nuance. Mangan et al found that IL-17A neutralization in imiquimod-induced skin inflammation models failed to reduce serum IL-22 levels, suggesting complex, context-dependent regulation.[16]

The clinical observation that brodalumab (IL-17RA antagonist) can induce eczematous eruptions highlights the functional diversity within the IL-17 cytokine-receptor system.[17] IL-17 family members contain six ligands (IL-17A-F) and five receptors (IL-17RA-RE) form distinct signaling complexes (Table 1). This molecular heterogeneity suggests that IXE/SEC may permit IL-17C/E-mediated Th2 inflammation. Brodalumab's broader inhibition might paradoxically suppress eczema pathways while treating psoriasis.[11,18]

Upon the first occurrence of paradoxical eczema in this patient, IXE injections were discontinued. Topical desonide cream and oral tripterygium wilfordii glycosides were administered for 4 weeks, with no significant improvement. Subsequent treatment with abrocitinib led to marked rash resolution within 14 days. However, psoriasis lesions recurred 7 days after abrocitinib cessation. Reintroduction of IXE triggered recurrent paradoxical eczema. After permanent discontinuation of IXE, the patient received upadacitinib. Both psoriasis and PE demonstrated significant improvement within 4 weeks of therapy.

PE significantly impacts therapeutic decision-making in psoriasis management. While some patients achieve PE remission with topical corticosteroids without discontinuing their original biologic therapy,[19] a substantial proportion require switching to alternative biologics. Notably, paradoxical eczema has been observed to persist or recur after biologic agent substitution.[4] Oral immunomodulators (eg, methotrexate), which simultaneously target both psoriasis and PE, may offer a viable alternative therapeutic strategy for these patients. TWG are derived from the traditional Chinese medicinal plant, consists mainly of triptolides, which have demonstrated significant anti-inflammatory and immunosuppressive properties.[20] As a result, it has been extensively employed in China for the long-term management of various inflammatory and autoimmune disorders, including psoriasis, eczema, systemic lupus erythematosus, rheumatoid arthritis, and Behçet's disease, as well as certain vasculitides.[21,22] However, therapeutic efficacy demonstrates considerable interpatient heterogeneity, with no reliable predictive biomarkers currently established.

Table 1 IL-17 Family Members and Biological Relevance

Receptors	Ligand Specificity	Biological Relevance
IL-17RA/RC	IL-17A, IL-17F	Psoriasis pathogenesis
IL-17RA/RB	IL-17E (IL-25)	Th2-mediated inflammation
IL-17RA/RE	IL-17C	Atopic eczema development

The Janus kinase and signal transducer and activator of transcription (JAK-STAT) pathway is an evolutionarily conserved membrane-to-nucleus signaling cascade that regulates gene transcription and immune responses. In recent years, targeting this pathway has emerged as a transformative strategy for managing AD and psoriasis.[23] Abrocitinib is a highly selective JAK1 inhibitor approved in China and internationally for moderate-to-severe AD in patients ≥12 years who are candidates for systemic therapy. It has also been evaluated in moderate-to-severe psoriasis.[24] Upadacitinib, an oral JAK1-preferential inhibitor with global approvals (FDA, EMA, etc.) for multiple chronic inflammatory diseases, including AD, psoriatic arthritis, ulcerative colitis, rheumatoid arthritis, shows broad therapeutic potential across immune-mediated conditions.[25]

Th2-polarized inflammation drives AD progression through cytokines IL-4, IL-5, IL-13, and IL-31. Key receptor–kinase interactions include IL-4R (JAK1/JAK3-coupled), IL-13R (JAK1/JAK2/TYK2-coupled). JAK1 inhibition disrupts downstream signaling of these cytokines, attenuating pruritus, epidermal barrier dysfunction, and Th2-mediated inflammation. The IL-17/IL-23 axis dominates psoriasis immunopathology, with critical contributions from IL-6 (JAK1/JAK2/TYK2-coupled), IL-22 (JAK1/TYK2-coupled) and IFN-γ (JAK1/JAK2-coupled). JAK1 blockade concurrently inhibits IL-17/23 pathway signaling and keratinocyte hyperproliferation. The shared JAK1 dependency in both AD and psoriasis pathogenesis provides a molecular rationale for using abrocitinib and upadacitinib in paradoxical dermatoses.[26]

The US Food and Drug Administration (FDA) has issued a boxed warning (its strongest safety alert) for JAK inhibitors based on safety data from rheumatoid arthritis clinical trials.[27–29] Key infection-related findings in patients with AD include herpes simplex virus (HSV) reactivation and herpes zoster. Tuberculosis (TB) reactivation was not reported in either abrocitinib or upadacitinib treated patients in 12- and 16-week study periods, respectively.[25]

Conclusion

Ixekizumab demonstrates robust efficacy in psoriasis, particularly for moderate-to-severe cases. As these agents gain broader use, paradoxical inflammatory reactions and secondary infections due to immunodeficiency are expected to rise. Upadacitinib rapidly resolved ixekizumab-induced paradoxical eczema with no adverse events during 1-month follow-up. Enhanced awareness and monitoring of such adverse events will optimize biologic therapy in clinical practice. Close monitoring remains essential to ensure patient safety.

Ethics Statement

The publications of images were included in the patient's consent for publication of the case. The Hospital Ethics Committees of the Fifth People's Hospital of Hainan Province approved to publish the case details.

Consent Statement

Informed consent was provided by the patient for publication of the case.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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